

CLAIMS

What is claimed is:

- 5 1. A method of determining how the solubility of a solid compound-of-interest is affected by its form during a period between the early-lead optimization and clinical trials, which comprises:
- (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of
10 the samples is different;
- (b) forming a liquid portion of each sample by adding a solvent to each sample;
 and
- (c) determining how much compound-of-interest dissolved in the liquid portion
 of each sample.
- 15 2. The method of claim 1, wherein:
- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is
20 analyzed to determine whether any change of form occurred;
- (c) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;
- (d) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;
- 25 (e) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;
- 30 (f) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

- (g) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;
- (h) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;
- (i) the amount of compound-of-interest is less than about 100 micrograms;
- (j) the amount of compound-of-interest is less than about 50 micrograms; or
- (k) the amount of compound-of-interest is less than about 10 micrograms.

3. A method of determining how the dissolution of a solid compound-of-interest is affected by its form, which comprises:

- (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;
- (b) forming a liquid portion of each sample by adding a solvent to each sample; and
- (c) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

4. The method of claim 3, wherein:

- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred; or
- (c) the method further comprises:
- (i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest in a first form;
- (ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest in a second form that differs from the first form;
- (iii) forming a liquid portion of each sample in the first sub-array by adding a controlled amount of a solvent to each sample in the first

- sub-array at a time point that is unique to each sample in the first sub-array;
- 5 (iv) forming a liquid portion of each sample in the second sub-array by adding a controlled amount of a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;
- 10 (v) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and
- (vi) determining how much compound-of-interest dissolved in the liquid portion of each sample;
- 15 (d) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;
- (e) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;
- 20 (f) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;
- (g) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;
- 25 (h) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;
- (i) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;
- 30 (j) the amount of compound-of-interest is less than about 100 micrograms;
- (k) the amount of compound-of-interest is less than about 50 micrograms; or
- (l) the amount of compound-of-interest is less than about 10 micrograms.

4. A method of determining how the stability of a solid compound-of-interest is affected by its form, which comprises:

- 5 (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;
- (b) exposing the compound-of-interest in each sample to a condition that may affect the stability of the compound-of-interest; and
- 10 (c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

5. The method of claim 4 wherein:

- 15 (a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;
- (b) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;
- 20 (c) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;
- (d) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the
- 25 second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;
- (e) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;
- 30 (f) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

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- (g) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;
 - (h) the amount of compound-of-interest is less than about 100 micrograms;
 - (i) the amount of compound-of-interest is less than about 50 micrograms; or
 - (j) the amount of compound-of-interest is less than about 10 micrograms.

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6. A method of determining how the hygroscopicity of a solid compound-of-interest is affected by its form, which comprises:

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- (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

- (b) exposing the compound-of-interest in each sample to a controlled relative humidity for a period of time; and

- (c) determining the change in water content of the compound-of-interest in each sample.

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7. The method of claim 6 wherein:

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- (a) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;
 - (b) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;
 - (c) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;
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- (d) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;
- 5 (e) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;
- (f) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;
- 10 (g) the amount of compound-of-interest is less than about 100 micrograms;
- (h) the amount of compound-of-interest is less than about 50 micrograms; or
- the amount of compound-of-interest is less than about 10 micrograms.

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8. A method of determining the effect of a condition on the solubility of a compound-of-interest, which comprises:

- (a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest and a solvent;
- 20 (b) exposing each sample to a condition that differs for at least two samples in the array; and
- (c) determining how much compound-of-interest dissolved in the liquid portion of each sample.

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9. The method of claim 8, wherein:

- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is
- 30 analyzed to determine whether any change of form occurred;

- (c) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;
- (d) the amount of compound-of-interest is less than about 100 micrograms;
- (e) the amount of of compound-of-interest is less than about 50 micrograms; or
- (f) the amount of compound-of-interest is less than 10 micrograms.
10. A method of determining the effect of a condition on the dissolution of a compound-of-interest, which comprises:
- (a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest and a solvent;
- (b) exposing each sample to a condition that differs for at least two samples in the array; and
- (c) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.
11. The method of claim 10, wherein:
- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;
- (c) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, or temperature;
- (d) the method further comprises:
- (i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest;

- (ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest;
- (iii) forming a liquid portion of each sample in the first sub-array by adding a solvent to each sample in the first sub-array at a time point that is unique to each sample in the first sub-array;
- (iv) exposing each sample in the first sub-array to a first condition;
- (v) forming a liquid portion of each sample in the second sub-array by adding a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;
- (vi) exposing each sample in the second sub-array to a second condition that differs from the first condition;
- (vii) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and
- (viii) determining how much compound-of-interest dissolved in the liquid portion of each sample;
- (e) the amount of compound-of-interest is less than about 100 micrograms;
- (f) the amount of of compound-of-interest is less than about 50 micrograms; or
- (g) the amount of compound-of-interest is less than 10 micrograms.

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12. A method of determining the effect of a condition on the stability of a compound-of-interest, which comprises:

- (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the controlled amount is less than about 100 μg ;
- (b) exposing each sample to a condition that differs for at least two samples in the array; and

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(c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

13. The method of claim 12, wherein:

- 5 (a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;
- (b) the amount of compound-of-interest is less than about 100 micrograms;
- 10 (c) the amount of of compound-of-interest is less than about 50 micrograms; or
- (d) the amount of compound-of-interest is less than 10 micrograms.

14. A method of determining the effect of a condition on the hygroscopicity of a compound-of-interest, which comprises:

- 15 (a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest;
- (b) exposing the compound-of-interest in each sample to a controlled relative humidity for a period of time and to an additional condition that differs for at least two
- 20 samples in the array; and
- (c) determining the change in water content of the compound-of-interest in each sample.

15. The method of claim 14, wherein:

- 25 (e) the condition is pH, ionic strength, counter-ion concentration, radiation, oxidative conditions, mechanical stress, or temperature;
- (f) the amount of compound-of-interest is less than about 100 micrograms;
- (g) the amount of of compound-of-interest is less than about 50
- 30 micrograms; or
- (h) the amount of compound-of-interest is less than 10 micrograms.

16. A method of determining the effect of an excipient on the solubility of a compound-of-interest, which comprises:

- (a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest, a solvent, and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples; and
- (b) determining how much compound-of-interest dissolved in the liquid portion of each sample.

17. The method of claim 16, wherein:

- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;
- (c) the amount of excipient in at least one sample is zero;
- (d) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;
- (e) the amount of compound-of-interest is less than about 100 micrograms;
- (f) the amount of compound-of-interest is less than 50 micrograms; or
- (g) the amount of compound-of-interest is less than 10 micrograms.

18. A method of determining the effect of an excipient on the dissolution of a compound-of-interest, which comprises:

- (a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest, a solvent, and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples; and
- (b) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

19. The method of claim 18, wherein

- (a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;
- (b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred; or
- (c) the method further comprising:
 - (i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest and a first excipient;
 - (ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest and a second excipient that differs from the first excipient and/or is provided in a different amount than the first excipient;
 - (iii) forming a liquid portion of each sample in the first sub-array by adding a solvent to each sample in the first sub-array at a time point that is unique to each sample in the first sub-array;
 - (iv) forming a liquid portion of each sample in the second sub-array by adding a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;
 - (v) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and
 - (vi) determining how much compound-of-interest dissolved in the liquid portion of each sample;
 - (d) the amount of excipient in at least one sample is zero;
 - (e) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;
 - (f) the amount of compound-of-interest is less than about 100 micrograms;

(g) the amount of compound-of-interest is less than 50 micrograms; or

(h) the amount of compound-of-interest is less than 10 micrograms.

20. A method of determining the effect of an excipient on the stability of a compound-of-interest, which comprises:

5 (a) preparing an array of samples, each of which comprises a controlled amount of the compound-of-interest and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples;

10 (b) exposing the samples to a condition that may affect the stability of the compound-of-interest; and

(c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

21. The method of claim 20, wherein:

15 (a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(b) the amount of excipient in at least one sample is zero;

20 (c) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;

(d) the amount of compound-of-interest is less than about 100 micrograms;

(e) the amount of compound-of-interest is less than 50 micrograms; or

25 (f) the amount of compound-of-interest is less than 10 micrograms.

22. A method of determining the effect of an excipient on the hygroscopicity of a compound-of-interest, which comprises:

30 (a) preparing an array of samples, each of which comprises a controlled amount of the compound-of-interest and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples;

(b) exposing the samples to a controlled relative humidity for a period of time; and

(c) determining the change in water content of the compound-of-interest in each sample.

23. The method of claim 22, wherein:

- 5 (g) the amount of excipient in at least one sample is zero;
- (h) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;
- (i) the amount of compound-of-interest is less than about 100 micrograms;
- 10 (j) the amount of compound-of-interest is less than 50 micrograms; or
- (k) the amount of compound-of-interest is less than 10 micrograms.